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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/758,033	11/27/1996	GARY L. CLAYMAN	INGN:022	5378

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	PAPER NUMBER
1632	
MAIL DATE	DELIVERY MODE
07/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	08/758,033	CLAYMAN, GARY L.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-14,16-20,26-32,36,37 and 146-150* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-14,16-20,26-32,36,37 and 146-150* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 November 1996* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The finality of the office action mailed on 09/25/2007 is withdrawn in view of the pre-appeal conference decision mailed on 04/09/2008. This is in response to Applicant's pre-appeal conference request filed on 02/22/2008. Prosecution on the merits resumes.

Previous claim amendments filed on 07/05/2007 have been entered. Claim 1-9, 11-14, 16-20, 26-32, 36, 37, and 146-150 are pending and currently under examination. Claim 146 has been amended.

This application, 08/758,033 filed on November 27, 1996, claims benefit of the provisional application 60/007,810 filed on 11/30/1995.

The rejection of claims 1-9, 11-14, 16-19, 26, 36, 37, and 146-150 under 35 U.S.C. 102(e) as being as being anticipated by Xu et al. (Xu et al., U.S. Patent 5,496,731 issued on March 5, 1996) as evidenced by Fung (U.S. Patent 6,590,086, issued July 8, 2003) and Donehower, 1994 (Tumor suppressor gene p53 and apoptosis, *The Cancer Bulletin* 46: 161-166, 1994) is withdrawn because upon further consideration Xu et al. does not teach all of the limitations of the claims

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 recites the limitation "said multiple injections" in "wherein said multiple injections comprise about 0.1-0.5 ml volumes spaced about 1 cm apart". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-9, 11-14, 16-20, 26-32, 36, 37, and 146-150 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over **Roth et al.** (US Patent 6,069,134, issued 05/30/2000) in view of **Langdon et al.** (Langdon et al., Expression of the tumour suppressor gene p53 in oral cancer. *Br J Oral Maxillofac Surg.* 30(4):214-20, 1992).

Claims 1 and 146 are directed to a method of inhibiting growth of (for claim 1)/inducing apoptosis in (for claim 146) a tumor cell expressing wild-type p53 in a human subject with a solid tumor comprising the steps of: (a) providing a viral expression construct comprising a promoter functional in eukaryotic cells and a polynucleotide encoding a functional p53 polypeptide, wherein said polynucleotide is positioned sense to and under the control of said promoter; and (b) parenterally administering said viral expression construct to said subject, the administration resulting in expression of said functional p53 polypeptide in cells of said tumor

and inhibition of tumor cell growth (for claim 1)/induction of apoptosis in the tumor cell (for claim 146).

Roth et al. teaches the use of tumor suppressor genes in combination with a DNA damaging agent or factor for use in killing cells, and in particular cancerous cells (See abstract and bridging paragraph, columns 4-5, Roth et al.). A tumor suppressor gene, p53, was delivered via a recombinant adenovirus-mediated gene transfer both in vitro and in vivo, in combination with a chemotherapeutic agent (See abstract and lines 25-35 and column 8, Roth et al.). Treated cells underwent apoptosis with specific DNA fragmentation (See abstract and lines 51-61, col. 29, Roth et al.). Direct injection of the p53-adenovirus construct into tumors subcutaneously, followed by intraperitoneal administration of a DNA damaging agent, cisplatin, induced massive apoptotic destruction of the tumors (See abstract and bridging paragraph, columns 7-8, Roth et al.).

More specifically, Roth et al. discloses following information that teaches the instantly claimed invention:

(i) A method of killing a tumor cell in a tumor of a human cancer patient by expressing functionally active p53 from a DNA construct (claims 1 and 3, Roth et al.), and the expression of p53 results in apoptotic destruction of the tumors (abstract and lines51-53, column 29) --- which teaches inhibiting growth of a tumor recited in claim 1 and inducing apoptosis recited in claim 146 of instant application via expression of functional p53;

(ii) The tumors are either malignant or benign (bridging paragraph, columns 3-4) and comprise human breast cancer, lung cancer (which encompasses H460 human lung tumor cells

that have a wild-type p53), sarcoma, melanoma, lymphoma, epithelial cancer carcinoma cancer (claims 30-39) --- which teaches various tumors recited in claims 2-5 of instant application;

(iii) The expression vector encoding p53 can be delivered by a variety of vectors including adenoviral vectors (claims 23-28, Roth et al.), replication-deficient wild-type p53 adenovirus (abstract, Roth et al.), adenovirus lacking E1 region (claims 52 and 53), with CMV IE promoter driving p53 expression (lines 53-61, column 6, claim 22) --- which teaches claims 6-9 of instant application;

(iv) Administer Ad5CMV-p53 *at least one time over a period of time* (claims 40, 41, 61-63), and in a small volume such as 10 ml *or less* (lines 55-64, column 31), ranging from $1x10^{10}$ to 5×10^{12} pfu as continuous perfusion over a period of time (col. 30, lines 42-57), tumor treatment protocol involves resection of tumor followed by administration of Ad5CMV-p53 (col. 31, lines 55-64) and patients receive at least two course of therapy (lines 20, col. 32). It is noted that volume of 10 ml or less (lines 55-64, col. 31) and the local intratracheal administration results in the delivery of recombinant p53 adenovirus closer to the site of the target cells (lines 61-63, col. 30) taught by Roth are broadly encompassed by the limitations "*about* 0.1- 0.5 ml" and "spaced *about* 1 cm apart" recited in claim 27 of instant application. Accordingly, the disclosure cited from columns 30-32 and claims 40, 41, 60-63 of Roth et al. teach the limitations of claims 11-14, 17, 18, 26, 27, and 37 of instant application;

(v) DNA construction administered to the tumor through a catheter, a syringe or directly into the tumor (claims 5-7, Roth et al.), intralesional injection and other parenteral routes of administration, such as intravenous, percutaneous, endoscopic, or subcutaneous injection (col. 8lines 1-9), and a tumor to be treated by said method can be resected endoscopically and that the

residual tumor site (i.e. the resultant body cavity formed by tumor excision) can then be injected with said expression vector (col. 31, lines 55-64) --- which teaches parentreal administration in claims 1 and 146 and claims 16,18, 36, and 147-150 of instant application.

(vi) Ad5CMV-p53 is formulated to a polylysine-glycoprotein (claim 45) and further comprises a polyadenylation signal (claim 46) --- which teaches continuous epitope tag recited in claims 19 and 20 of instant application.

(vii) The treatment method further comprise contacting tumor with DNA damaging agent (claim 42), comprises □-irradiation, X-ray, UV-irradiation (col. 4, lines 61), chemotherapeutic (claim 14), which includes camptothecin, veramil, adriamycin, podophyllotoxin, actinomycin-D, and mitomycin-C (claims 64-69) --- which teaches claims 28-32 of instant application;

(viii) Administer an adenovirus encoding tumor suppressor p53 to H460 human lung tumor cells that have a wild-type p53 (lines 51-55, col. 25, lines 39-40, col. 11, and Fig. 7C, Roth et al.) --- which teaches administration of functional p53 to a tumor cell line expressing wild-type p53.

Roth et al. does not teach "a tumor cell expressing wild-type p53 in a human subject with a solid tumor" recited in claims 1 and 146 of instant application.

However, Langdon taught squamous cell carcinomas (SCC) of humans had wild-type p53 and a mixture of mutated and wild-type p53, which teaches "a tumor cell expressing wild-type p53 in a human subject with a solid tumor" as claimed. When mutated p53 is expressed in SCC, it may only be expressed in "focal areas of positive cells" (see Abstract). "p53 was found to be present throughout the tumour or to consist of groups of positive cells scattered among negative

cells" (pg 217, sentence bridging col. 1-2). Thus, tumor cells, such as SCC, were known in the art at the time of filing and were known to express wild-type p53 as claimed.

Thus, it would have been obvious to those of ordinary skill in the art at the time the invention was made to parenterally administering a tumor in a patient with a viral vector encoding a p53 operably linked to a promoter, taught by Roth et al, wherein the tumors were squamous cell carcinomas expressing wild-type p53 in a patient as described by Langdon et al. Those of ordinary skill in the art at the time of filing would have been motivated to treat the squamous cell carcinomas described by Langdon by the methods described by Roth, which leads regression of the squamous cell carcinomas and prevent death in the patient.

There would have been a reasonable expectation of success given (i) successful demonstration of a method of inhibiting tumor cell growth via induction of apoptosis in the tumor cells by parenterally administering the tumor in a human patient with a viral vector encoding a p53 operably linked to a promoter, by the teachings of Roth et al., and (ii) the demonstration of squamous cell carcinomas, a human head and neck oral cancer, expresses wild-type p53 by the teachings of Langdon et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA

1970); and, In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1-14, 16-20, 26-32, 36, 37 and 146-150 remain provisionally rejected under the judicially created doctrine of double patenting over claims 26, 29, 58, 89 of copending Application No. 09/968,958. Previous provisional rejection is ***maintained*** for the reasons of record advanced on pages 19-20 of the Non-Final office action mailed on 03/07/2007.

Applicant's arguments

(i) With regard to claims 1-14, 16-20, 26-32, 36, 37 and 146-150 being provisionally rejected under the judicially created doctrine of double patenting over claims 26, 29, 58, 89 of copending Application No. 09/968,958, Applicant argues that, if a provisional double-patenting rejection is the only rejection remaining in an application, the Examiner should withdraw the rejection and permit the application to issue as a patent. MPEP § 804(I)(B), p. 800-15. After one application issues as a patent, the provisional double-patenting rejection in the remaining application is converted to an actual double patenting rejection. Id. Applicant states that once either the present application or the '958 application issues as a patent, Applicant will file a terminal disclaimer, if appropriate, in the remaining pending application.

(ii) With regard to the Non-Final office action indicating that if claim 1 is found to be allowable, claim 146 will be objected to under 37 C.F.R. § 1.75 as being a substantial duplicate thereof, Applicant argues that the Action considers claim 146 as merely reciting a mechanism by which the method of claim 1 works. Applicant notes that such an objection would be improper. As stated in MPEP § 706.03(k), "court decisions have confirmed applicant's right to restate (i.e., by plural claiming) the invention in a reasonable number of ways. Indeed, a mere difference in scope between claims has been held to be enough." The scope of the phrases "inhibition of tumor cell growth" (recited in claim 1) and "induction of apoptosis" (recited in claim 146) are not identical.

Response to Applicant's arguments

(i) The Examiner notes that the provisional rejection of claims 1-14, 16-20, 26-32, 36, 37 and 146-150 under the judicially created doctrine of double patenting over claims 26, 29, 58, 89 of copending Application No. 09/968,958, is NOT the only rejection remained in the instant application.

In the instant case, the method set forth in claim 1 of the instant application is essentially the same as that set forth in claims 29 and 58 of '958. Further, it is noted that claim 26 of application 09/968,958 encompasses essentially the same invention as encompassed by claims 1 and 146 of 08/758,033. Dependent claims in each application set forth specific types and amounts of vectors, specific types of cancers, and specific times of administration that set forth inventions, which are essentially the same in breadth between both applications.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

(ii) Applicant's arguments regarding the statement, should claim 1 be found allowable, claim146 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof, was found persuasive. *The objection of claim 146 being substantial duplicate of claim 1 is withdrawn.*

4. Claims 1-14, 16-20, 26-32, 36, 37 and 146-150 are newly provisionally rejected under the judicially created doctrine of double patenting over claims 58-62, and 65, 66, 107, and 108 of copending Application No. 10/395,864.

Both instant application and copending Application No. 10/395,864 reads on treating cancer cell expressing wild-type p53 via expressing a functional p53 from a viral vector. The method set forth in claims 1 and 146 of the instant application encompasses the method of treating cancerous lesion in a mouth recited in independent claim 60 of 10/395,864. Furthermore, the specification of instant application discloses treating cancer in a mouth (See for instance, page 68, Table 6).

5. Claims 1-14, 16-20, 26-32, 36, 37 and 146-150 are newly provisionally rejected under the judicially created doctrine of double patenting over claims 26-89 of copending Application No. 09/968,958.

Instant application reads on treating cancer cell expressing wild-type p53 via expressing a functional p53 from a viral vector. Co-pending application 09/968,958 reads on treating respectable tumor via expressing a functional p53 from a viral vector. Furthermore, the specification and claim 18 of instant application reads on treating residual tumor remains after tumor excision. The claimed invention of instant application is an obvious variant of claims 26-89 of copending Application No. 09/968,958.

Conclusion

6. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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